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Immune reconstitution inflammatory syndrome (IRIS) in the developing world

Increasing Frequency of IRD/IRIS

Reports of IRD/IRIS first surfaced when ART gradually came into use in the developed world. However, it only seemed to affect a small minority of people there - possibly because ART is generally started well before advanced disease. Some reports dismissed most IRD/IRIS as transient - even as a good sign of improving health. The contribution of IRD/IRIS to the burden of serious illness in people with AIDS is only now being re-evaluated as its frequency is increasing now that ART is being introduced in resource-limited settings.

According to a review recently published by French et al in AIDS (18(12):1615-1628, 2004.): "The increasing use of HAART in developing countries will inevitably result in a large number of severely immunodeficient patients being given HAART. There will therefore be many patients at-risk of developing IRD."

(This review is available online:

<http://www.medscape.com/viewarticle/487529>)

A quick survey of HATIP's advisory panel suggests this is already the case.

"We are embarking on the national rollout programme in South Africa," said Dr Francesca Conradie of Johannesburg. "We are now starting over 100 patients a week in our hospital. [These are] very ill patients often with CD4 counts below 100.

She described a number of reactions she has seen and notes that "this syndrome is proving to be the most important cause for morbidity in patients on ARVs."

Chris Green of Indonesia concurs: "We are certainly experiencing this syndrome, although I think it is perhaps rarely correctly identified."

Dr. Gerard van Osch of St. Maarten says: "I notice that not only the "dangerous/serious" opportunistic infections could flare up, but also flare ups of more mild but debilitating problems."

Other panel members also described their experience with IRD/IRIS (see IRD/IRIS by OI below).

Who is at greatest risk of IRD/IRIS?

According to HATIP advisor Dr. Francois Venter of Johannesburg, South Africa: "CD4<50 is the biggest clue of a patient's risk."

This is most true of the more serious events. However, some patients with higher CD4 cell counts at the start of treatment may still develop certain IRD/IRIS disorders - especially skin problems.

Any patient with an active opportunistic infection or previously-treated opportunistic infection (debris left behind by a prior cured infection such as cryptococcal meningitis and CMV can trigger IRD/IRIS) is at risk. As already noted, the infection may be sub clinical, so this risk factor is not always so helpful.

Studies suggest that inherited differences also influence a person's susceptibility to IRD/IRIS. This is true both for IRD/IRIS associated with certain infections (such as MAC or TB) and IRD/IRIS associated with autoimmune disorders. Currently, this is difficult to screen for in most settings, and thus, virtually irrelevant.

Recognising/diagnosing IRD/IRIS

Clearly, IRD/IRIS is temporally related to initiating ART, with most events occurring in the first couple of months after beginning treatment. However, some reactions may happen months later (some of this is related to nature of opportunistic infection triggering IRD/IRIS). Data are also accumulating with long term follow-up, suggesting that some IRD/IRIS illnesses are biphasic, with an initial reaction occurring the first few weeks or months after treatment begins, and a related event (in the same location or tied to the same infection) occurring months or years later - in otherwise stable, healthy patients.

IRD/IRIS can result from a wide variety of infections or illnesses, including some not so commonly diagnosed in people with HIV. This can make recognising IRIS very difficult, particularly in settings where healthcare providers and caregivers have limited experience and/or facilities to diagnose and treat opportunistic infections. A distinction also must be made between IRD/IRIS/ associated with an infectious cause and those associated with an autoimmune disorder (see later in this piece).

As ART is rolled out in other parts of the globe, the illnesses associated with infectious IRD/IRIS will most likely reflect diseases that are endemic to a region. For example, a recent report in the Archives of Dermatology (2004 Aug; 140 (8):997-1000) describes three cases of IRIS associated with leprosy in French Guiana and Martinique. In South Africa, Dr. Francois Venter says "the diseases we see are remarkably similar to those seen in the US [CMV, MAI, shingles], although we see more cryptococcal meningitis and TB [IRD/IRIS].

But despite the variety of infections associated with IRD/IRIS, some patterns have emerged that can help caregivers distinguish between IRD/IRIS and an ordinary opportunistic infection. These have permitted French et al to propose the following preliminary criteria for the diagnosis of infectious IRD/IRIS in HIV patients on antiretroviral therapy. A diagnosis of IRD would require both major criteria or criterion A and two minor criteria.

Major criteria

1. An unusual presentation of 'opportunistic infections or tumours' in patients responding to antiretroviral therapy (ART).

- Localised disease, for example, the infection seems focused on the lymph nodes, liver or spleen
- An exaggerated inflammatory reaction, for example
- Severe fever, with exclusion of other causes
- Painful lesions
- An unusual inflammatory response in affected tissues, e.g. Granulomas (tumours with rough grainy texture), suppuration (the formation of pus abscesses), necrosis (tissue death), microscopic evidence of inflammatory cells invading the tissue

2. Progression of conditions that were successfully treated prior to ART with organ dysfunction or enlargement of pre-existing lesions and exclusion of treatment toxicity and new diagnoses for example:

- Development or enlargement of cerebral space-occupying lesions after treatment for cerebral cryptococcosis or toxoplasmosis
- Progressive or new pneumonia after successful treatment for pulmonary MTB or PCP
- New onset or worsening of uveitis/vitritis after the resolution of CMV retinitis

- Fever and cytopenia (cell death) after treatment for disseminated MAC
 - Enlargement of Kaposi's sarcoma lesions and subsequent resolution or partial regression without commencement of radiotherapy, systemic chemotherapy or intralesional therapy
3. Decrease in plasma HIV RNA level by $>1 \log_{10}$ copies/mL

Minor criteria

- Increased blood CD4 T-cell count after ART.
- Increase in an immune response specific to the relevant pathogen, e.g. DTH response to mycobacterial antigens
- Spontaneous resolution of disease without specific antimicrobial therapy or tumour chemotherapy with continuation of antiretroviral therapy

Features of IRD/IRIS by opportunistic infection

Despite the patterns noted above, the symptoms of IRIS to some extent depend on the infection or illness with which it is associated because some disease-causing mechanisms are determined by the pathogen.

Some IRD/IRIS is dependent upon a CD4-cell mediated response to existing infections (which kicks into gear when CD4 cell numbers rise). Others depend on other immune cells responses to antigens (foreign particles - possibly from a now dead microbe). This finding may determine the timing of symptoms as well as provide clues to the diagnosis and management of the condition.

For example, restoration of a DTH response (positive skin test) is a common finding in patients with IRD/IRIS triggered by mycobacteria (TB, MAC, leprosy).

Unfortunately, this article can only serve as a brief introduction to IRIS. We hope to describe some of the IRIS reactions seen with specific opportunistic infections in more detail in upcoming issues. A number of excellent review articles have been published online (see References below).

TB

Patients co-infected with HIV and *Mycobacterium tuberculosis* (tuberculosis or TB) who are receiving HAART and drugs against tuberculosis may develop severe inflammatory reactions including fever, worsening of pulmonary conditions, shortness of breath, and enlargement of lymph nodes or cerebral masses (tuberculomas). It presents within the first 2 months of HAART, usually in the first 2-3 weeks.

Given the importance of TB coinfection in HIV disease and the apparent frequency of TB IRD/IRIS, we intend to cover TB in much greater detail before the end of this year.

Dr Francesca Conradie: "While we actively pursue the diagnosis of TB, we still have to admit about 2 patients a week with [TB IRD/IRIS]. We have had at least a single fatality from the condition. The patients have presented with pleural effusions and other CXR changes. They have developed new lymphadenopathy. We have also had to diagnose TB on bone marrow aspirate and trephine."

Chris Green: "We also had a case of recurrence of TB-like symptoms after almost six-months on ART, which I witnessed, that ended in death. The patient had been doing well for four months or so. Doctors put it down to poor adherence, but the patient was a nurse, and strongly maintained that he had been adherent."

Dr. Paul Roux, Cape Town: "We have been fortunate in seeing few cases of IRIS presenting as pulmonary TB. We have a high prevalence of tuberculosis in Cape Town, so children are screened

quite carefully. Many of those who started ARVs early on in our programme had been followed for up to 3 years before starting treatment. Given the difficulty of making a firm diagnosis of pulmonary tuberculosis in children, we probably err on the side of over-treatment. We had also been following our earliest ARV candidates for up to 3 years before starting ARVs."

Dr. Douglas Wilson, KwaZulu Natal, South Africa: "IRIS (or IRD) manifesting as a tuberculosis syndrome when the patient is already on treatment is a bit of a dilemma, especially when it flares up in a 'difficult to get at' area like the pericardium [the membrane around the heart]. Apparently the braver HIV clinicians will just treat with prednisone and not extend the duration of antituberculous therapy; my practise at the moment is to add another three months TB therapy as it is not possible to know whether the immune system is reacting against viable mycobacteria or just 'antigen debris'."

MAC

Mycobacterium avium intracellular complex (MAI or MAC) has not been widely perceived as a serious opportunistic infection in most resource-limited settings, because it is such a late-stage disease event that patients usually die of other causes before developing MAC symptoms.

That is changing with the introduction of ART and IRD/IRIS. Apparently, MAC infections are often present without leading to symptoms, but while symptomatic MAC pre-ART was generally a systemic disease (often associated with a non-specific form or wasting), MAC IRIS is usually localised, focusing on one part of the body. It may cause swollen or inflamed lymph nodes or organ. It might also merely cause ulcers in the gastrointestinal tract or skin abscesses.

Dr Francesca Conradie: "The other most important condition that we see is MAI. These patients present with organomegaly [swollen organs] and anaemia."

Other mycobacterial conditions:

Other mycobacteria also are able to trigger IRD/IRIS, including leprosy and, bizarrely, bacille Calmette-Guerin, mycobacteria bovis, which is used in BCG vaccinations used to prevent TB. Several cases of BCG lymphadenitis have been reported in children with HIV post-ART.

Dr. Paul Roux: "In infants under 12 months of age we have also seen a number of BCG ulcers, associated axillary adenopathy, abscess and fistula formation. These have responded fairly slowly to anti-tuberculous therapy."

Hepatitis

Worsening of viral hepatitis has been observed in persons with both known and previously undiagnosed viral hepatitis.

Dr. Halima Dawood, KwaZulu-Natal, South Africa: "Another manifestation of IRIS appears to be abnormal liver functions and it is difficult to determine if this is due to the ARVs or another infection, for example hepatitis B, CMV or disseminated tuberculosis."

Eye problems

There have been reports of new types of eye problems, usually CMV-related such as uveitis (inflammation of the iris, or entire eye) or inflammation within the back part of the eye (vitritis), among people who had previously been treated for CMV retinitis within a year of starting ART. This condition is caused by immune reactions

against inactive CMV in the eye, rather than by CMV itself. Nevertheless, it can cause loss of sight.

Since the CMV is usually dead, the approach to treatment is a quandary. It may be possible to treat these conditions with immune-suppressing steroids but some fear this could encourage CMV itself to reactivate.

CMV is not the only infection that can cause these eye problems. Other possible causes include histoplasma, leishmania, and possibly herpes zoster.

Chris Green: "We have one case currently of CMV following several months on ART. The doctors are unclear how to treat. It is extremely depressing for patients, families, activists and health care workers to experience this type of response to ART, resulting often in death, or in this case, partial blindness."

Dermatological conditions:

In some studies, the majority of IRD/IRIS events were due to the occurrence of dermatological problems including genital herpes simplex (HSV), genital and oral warts (HPV), molluscum contagiosum, and outbreaks of shingles (VZV). Perhaps the most unusual reaction reported is a severe skin rash in response to ten-year-old tattoos two months after starting ART.

Herpes viruses (HSV and VZV) are distinct from some of the other infections associated with HIV because they have little relation to CD4 cell count. Several studies show a dramatic increase in shingles in HIV-infected patients treated with ART, with the greatest risk in the first four months of therapy. Activation of shingles is related to the absolute increase in CD8+ T-lymphocytes.

Dr. Paul Roux: "What we did see in a cohort of 40 children was an increase in the number of children with flares of herpes simplex."

Dr Francesca Conradie: "We have seen many minor ones. They include molluscum contagiosum and oral hairy leucoplakia."

Dr. Gerard van Osch has seen "seborrheic eczema and allergic conjunctivitis [in a] patient [who has] already suffered from this condition in the past (giving rise to rashes in, for instance, the face which gives the appearance that the patient is very ill, while immune system is improving)."

Dr. Francois Venter: "I think the skin inflammation often seen post initiation [of ART] may be mild variations of IRD/IRIS."

Dr. Douglas Wilson: "I agree that inflammatory skin conditions are common, especially pruritic [itchy] papular eruption [pimples] and an inflammatory response to dermatophyte [skin/nail fungus such as tinea] infections."

Pneumocystis pneumonia (PCP)

New or recurrent pneumonia has been observed in a number of studies. It is standard practice to administer corticosteroids to patients with moderate-to-severe PCP, to decrease the inflammatory response to dying organisms.

Dr. Paul Roux: "We have seen an apparent increase in mild upper and lower respiratory tract infection [non-TB]."

Neurological IRD/IRIS

Inflammation and lesions of the central nervous system are of particular concern because they may result in permanent neurological disability or death. The condition could be triggered by a wide variety of organisms, including CMV, toxoplasmosis, cryptococci and other fungal organisms, JC virus/PML, TB, B19 Parvovirus and perhaps even HIV itself.

Often the original infection is cured, but the demyelination (loss of nerve cell coating) and swelling worsens in the CNS.

Dr. Douglas Wilson: "I have only lost one patient from IRIS - she developed extensive CNS toxoplasmosis (probable diagnosis) two months after starting ART, at a time when her viral load was undetectable and her CD4 count had risen from 40 to 80."

Cancer

Rapid progression, development and spread of cancerous lesions or tumours have been reported in patients responding to ART. It is postulated that these growths are an IRD/IRIS response to the viruses that trigger these cancers, for example, Non-Hodgkin's lymphoma (NHL) in response to Epstein-Barr Virus or Kaposi's sarcoma or multicentric Castleman's disease in response to HHV8.

Molly Tumusiime in Kampala, Uganda: "Patients starting ART and especially those whose CD4s are very low have been observed to get illnesses, for example, Kaposi's sarcoma, where minor lesions were observed to become severely aggressive."

Autoimmune and other miscellaneous disorders

There is increasing evidence that immune reconstitution can lead to autoimmune or inflammatory diseases such as lupus, Grave's disease, Reiter's Syndrome, Guillain-Barré syndrome, appendicitis, arthritis and sarcoidosis.

Sarcoidosis is granular inflammation (lesions, or raised red patches) of the lungs, skin and other organs, which is typically associated with infiltration of tissue by CD8 cells, but in patients on ART is caused by CD4 cell infiltrates.

Corticosteroids and other anti-inflammatory medications are the most likely treatment for such disorders, but it is important to first exclude infectious organisms as the cause of one of these orders.

Management

The best approach to management of IRD/IRIS is unclear. Treatment will likely differ by the causal infection but treating the associated infectious organism does not always lead to clinical improvement (particularly for culture negative infections). Reports of successful treatment are anecdotal. Since many cases resolve on their own it is impossible to say what works without conducting prospective clinical studies.

In all but the most serious cases, antiretroviral therapy should be continued - although there may be extreme cases where ART should be stopped temporarily until the patient has stabilized.

Anti-inflammatory medications may help decrease symptoms during the intense inflammatory phase but routine use of corticosteroid therapy is not yet defined. Other anti-inflammatory medications that target specific inflammatory cytokines (such as pentoxifylline and thalidomide) may also have a role, particularly for treating mycobacteria-related IRD/IRIS.

Dr. Halima Dawood, KwaZulu-Natal, South Africa: "The major difficulty is distinguishing active disease that requires therapy from an inflammatory reaction that requires non-steroidals and/or corticosteroids."

"Beyond this, it is important to alert caregivers in resource-limited settings to monitor those patients most at risk for IRD/IRIS, and inform their patients about what to watch for."

Molly Tumusiime: "There's need for closer monitoring during this initial phase before a patient starting ARVs can start getting longer intervals between appointment dates."

Chris Green: "Clearly, we all need more clear information in a much more accessible form to help doctors to identify and treat patients with IRIS, and for treatment activists to understand and prepare for this type of response."

Dr. Francois Venter: "Interestingly, many patients see the milder IRIS symptoms as side effects of the medication. It is important that they understand it's not. I explain it as "the body cleaning up all the things that have been growing unnaturally. I use [the analogy of a] thorn under the skin, with pus and inflammation being a way of getting rid of the thorn. Patients respond well to this, and are more prepared to put up with the symptoms."

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about HATiP

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The newsletter is edited by Theo Smart (Cape Town) and Keith Alcorn, NAM's Senior Editor (London).

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